N94-11557

PHYSIOLOGIC MECHANISMS OF CIRCULATORY AND BODY FLUID LOSSES IN WEIGHTLESSNESS IDENTIFIED BY MATHEMATICAL MODELING

K.E. Simanonok, R.S. Srinivasan[1], and J.B. Charles[2]

Universities Space Research Association
[1]KRUG Life Sciences
[2]Space Biomedical Research Institute
Johnson Space Center, Houston, Texas 77058

ABSTRACT

Central volume expansion due to fluid shifts in weightlessness is believed to activate adaptive reflexes which ultimately result in a reduction of the total circulating blood volume. However, flight data suggests that a central volume overdistention does not persist, in which case some other factor or factors must be responsible for body fluid losses. We used computer simulation to test the hypothesis that factors other than central volume overdistention are involved in the loss of blood volume and other body fluid volumes observed in weightlessness and in weightless simulations, and to identify these factors. The results predict that atrial volumes and pressures return to their pre-bedrest baseline values within the first day of exposure to head down tilt (HDT) as the blood volume is reduced by an elevated urine formation. They indicate that the mechanism for large and prolonged body fluid losses in weightlessness is red cell hemoconcentration that elevates blood viscosity and peripheral resistance, thereby lowering capillary pressure. This causes a prolonged alteration of the balance of Starling forces, depressing the extracellular fluid volume until the hematocrit is returned to normal through a reduction of the red cell mass, which also allows some restoration of the plasma volume. We conclude that the red cell mass becomes the physiologic driver for a large "undershoot" of body fluid volumes after the normalization of atrial volumes and pressures.

INTRODUCTION

The circulation and fluid distribution of the human body appear to be immediately and profoundly affected by exposure to weightlessness; blood and interstitial fluid which normally tend to pool in the legs due to gravity become redistributed toward the head (Leach, 1979, Epstein et al., 1980). This causes head congestion, headaches, facial edema, and stimulates a loss of water and electrolytes from all body water compartments through thirst depression and/or renal excretion.

While the measurement of many fluid shift responses in space has proven elusive, and inflight fluid shift data remain somewhat conflicting (Leach, 1987), some valuable measures of responses to weightlessness exist. Blood moves centrally within seconds upon exposure to weightlessness from the standing or sitting position, as measured by changes in the electrical impedance of the thorax during 20 seconds of weightlessness in parabolic flight (Mukai, 1991). In the first few days inflight there is an elevation of hemoglobin concentration (Kimzey, 1977) coincident with a weight loss primarily reflecting a negative water balance. Most of this loss occurs within the first three or four days (Thornton et al., 1987; Nicogossian and Parker, 1982; Thornton and Ord, 1977). Plasma volume decreases rapidly over hours and red cell mass decreases over weeks in space (Thornton et al., 1987; Nicogossian, 1985). These responses to fluid shifts are considered an adaptation to the central circulatory overdistention caused by fluid shifts in weightlessness (Nixon et al., 1979; Charles and Bungo, 1986; Leach, 1987). The final adapted state includes a reduced blood volume, with normal composition eventually regained (Nicogossian, 1985). However, recent results from the SLS-1 mission indicate that some body fluids do not simply decline to new equilibria but that they decrease rapidly to a low point and then begin some recovery (Leach et al., 1992). This "undershoot" of body fluid volumes has also been shown by our previous computer simulations to precede the final cardiovascular adaptation to fluid shifts (Simanonok et al., 1991, 1992).

The fact that fluid shifts probably begin before launch as astronauts wait in the semisupine position (Lathers, 1989) complicates the fluid shift picture, but the net effects on postflight fluid balance are probably not greatly different as a result of the pre-launch posture. Inflight measures of central venous pressure (Kirsch et al., 1984; Gaffney, 1992), suggest that central volume expansion in weightlessness may be very transient, or perhaps masked by physiologic responses to the pre-launch posture and acceleration to orbit. It is likely that several hours in the semisupine position allows time for the physiologic responses to fluid shifts to cause decreases in the astronauts' plasma volumes, actually beginning the long process of cardiovascular adaptation to weightlessness while on the ground.

Logically, if the central hypervolemia produced by a fluid shift could be reduced, then the physiologic responses resulting in fluid losses in weightlessness should also be reduced through a damping of the endocrine, neural, and hemodynamic mechanisms activated by fluid shifts. This concept has been experimentally validated in two water immersion experiments (Simanonok and Bernauer, in review; Simanonok, in review) and theoretically analyzed in computer simulation studies (Simanonok et al., 1991, 1992). Therefore, what may appear at first glance to be a counterintuitive countermeasure--reducing body fluid losses by removing body fluid beforehand--shows promise as a potential method to conserve body fluid volumes and return astronauts to earth in better condition that at present. Simulation results suggest that preadapting the circulation could help to conserve body fluid volumes for weightless exposures of 20 to 30 days duration (Simanonok et al., 1991, 1992).

The purpose of this study was to examine the mechanisms which could explain the loss of body fluids in weightlessness and how the preadaptation countermeasure could act to reduce the magnitude of body fluid losses. We hypothesized that factors other than central volume overdistention could be responsible for the loss of blood volume and other body fluid volumes observed in weightlessness and in weightless simulations. The assumption was made that the physiology of HDT provides a reasonably accurate analog of weightless exposure. This paper describes our progress to date in identifying the primary determinants or "drivers" of the physiologic adaptation of the human body to reduced fluid compartment volumes in weightlessness.

METHODS

A mathematical model derived from the Guyton Model of Fluid, Electrolyte, and Circulatory Regulation (Guyton et al., 1972) was used for this study. The model incorporates known relationships between physical, neural, and hormonal regulators of fluid balance and volume, pressure, and flow in the human circulation and body fluid compartments. It has been modified for weightless simulation by HDT by White (1974), with improvements by Leonard and Grounds (1977). It has been validated by comparison with data from both ground-based and flight experiments (Leonard et al., 1979, 1986).

We modified the model further as described previously (Simanonok et al., 1991) to enable long term simulation with eventual adaptation of the blood and other body fluid compartments to lower volumes during prolonged six-degree HDT. Also, provision was made to enable simulation of blood volume reduction by bleeding. With these modifications, the model was validated for its response to acute hemorrhage by comparing hematocrit changes with experimental hemorrhage data from human subjects (Simanonok, unpublished data).

The difference between the starting supine blood volume before HDT and the equilibrium blood volume after 70 days of HDT was taken as the volume to remove from circulation to preadapt the circulation to fluid shifts. Then another simulation of HDT was run after removal of the preadaptation volume, which was 534 ml, or about 11% of the starting blood volume.

RESULTS AND DISCUSSION

Data in the Figures are plotted on a logarithmic time scale so that all phases of the experiment out to 70 days may be distinguished. Each of the two experiments, head down tilt alone (HDT) or HDT preceded by blood volume reduction (BV REDUCTION + HDT, or PREADAPTED) began with a 30 minute period of baseline supine posture before the assumption of HDT. During the last 18 minutes of the 30 minutes of supine posture during BV REDUCTION + HDT, the

simulated subject was bled at a constant rate of 29.67 ml/min to preadapt the circulation to fluid shifts. This acute change in blood volume due to preadaptation is shown in Fig. 1; the naturally-adapting HDT blood volume falls below the PRE-ADAPTED blood volume after 10 hours and remains slightly less than the PREADAPTED blood volume until the two converge at about 70 days.

The rapid reduction of blood volume in HDT is due to an early decrease in the plasma volume (Fig. 2), which results from an increase in the urine flow (Fig. 3). The initially high urine flow results from increased renal blood flow, glomerular filtration, and appropriate endocrine responses (not shown).

Central vascular engorgement that is believed to occur due to fluid shifts in weightlessness is shown by atrial pressures (Fig. 4) and volumes (Fig. 5) increasing early in HDT, accounting for the increased stroke volume (Fig. 6) and cardiac output (Fig. 7). These expected early responses to fluid shifts show how hydraulic and endocrine factors rapidly act to elevate urine flow and deplete plasma volume. However, atrial volumes and pressures, stroke volume, and cardiac output are all decreased below baseline pre-HDT values within the first day of exposure to fluid shifts. This indicates a lack of a continuing central volume expansion driving the process of circulatory adaptation, and suggests involvement of another mechanism or mechanisms.

Fig. 1. Blood Volume

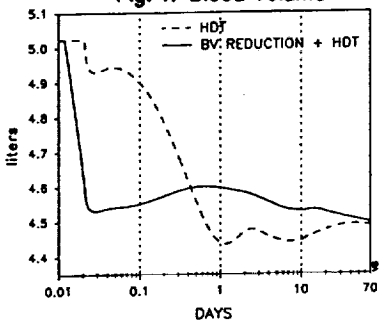


Fig. 2. Plasma Volume

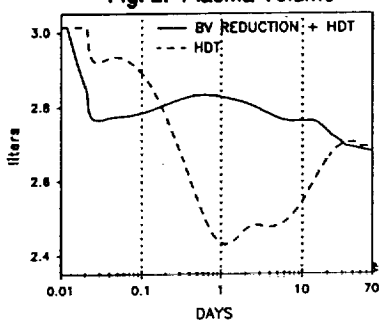


Fig. 3. Urine Flow

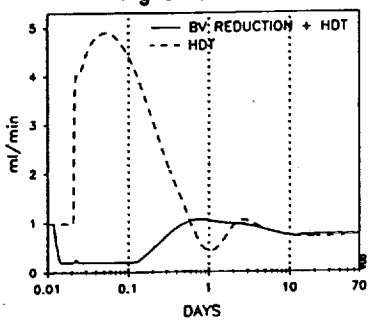


Fig. 4. Atrial Pressures

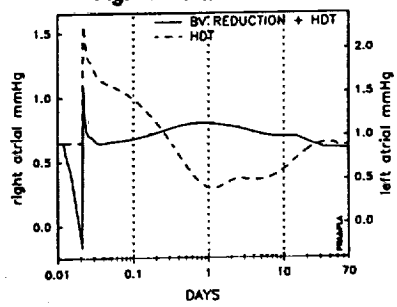


Fig. 5. Atrial Volumes

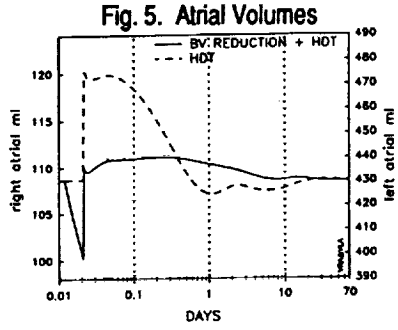


Fig. 6. Stroke Volume

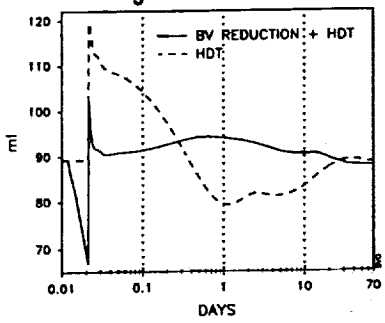
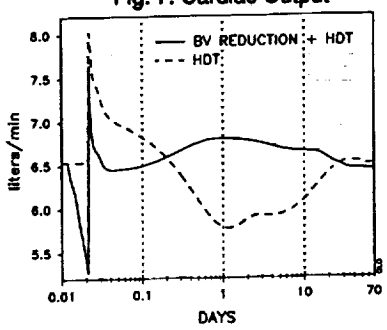
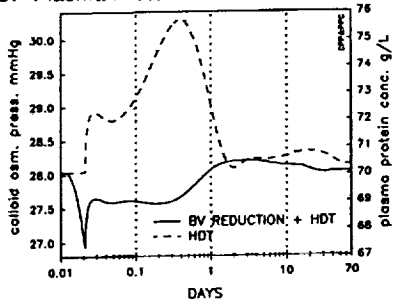


Fig. 7. Cardiac Output



As the plasma volume is decreased by an elevated urine flow, cells and protein concentrate in blood because they are much more slowly eliminated than water and electrolytes. The plasma protein concentration is increased, elevating the plasma colloid osmotic pressure (Fig. 8). This would tend to shift the balance of Starling forces toward net reabsorption, which could explain some initial transfer of fluid from other compartments into circulation. However, the plasma protein concentration is rapidly regulated again at nearly baseline concentrations by Day 2 of HDT, therefore hemoconcentration of protein cannot be a primary driver for more prolonged losses of body fluids. Also, the interstitial colloid osmotic pressure (Fig. 9) rises by almost the same amount in the first two days, which would tend to offset fluid movement caused by an elevated plasma colloid osmotic pressure. In fact, the interstitial colloid osmotic pressure remains elevated for some time after the plasma colloid osmotic pressure returns to near baseline.

Fig. 8. Plasma Protein and Colloid Osmotic Pressure



Hemoconcentration of red cells elevates the hematocrit and therefore the viscosity of blood (Fig. 10), which remain high until the red cell mass can be reduced (Fig. 11). An increased viscosity of blood increases the resistance to flow, thereby elevating the total peripheral resistance (Fig. 12). Because this is a precapillary resistance, the capillary pressure is decreased (Fig. 13) until the total peripheral resistance returns to baseline through a reduction of the red cell mass. The interstitial fluid pressure (Fig. 14) is not reduced by the same magnitude, so the net balance of Starling forces is shifted toward a reduced transcapillary pressure and flux (Fig. 15). This causes a depletion of the extracellular fluid volume. It is important to note that there is a large recovery from the "undershoot" of total extracellular fluid when adaptation is complete (Fig. 16).

Fig. 9. Intersitial Fluid Colloid Osmotic Pressure

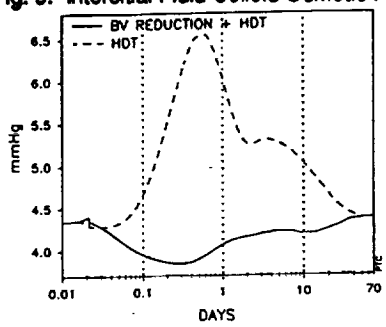


Fig 10. Hematocrit and Viscosity of Blood

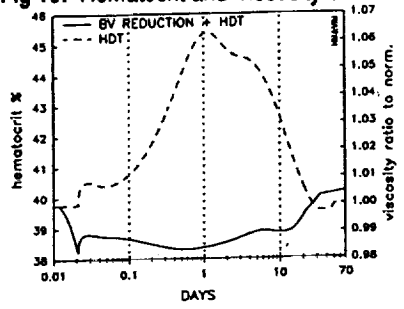


Fig. 11. Red Cell Mass

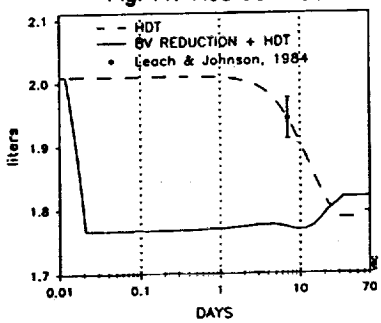


Fig. 12. Total Peripheral Resistance

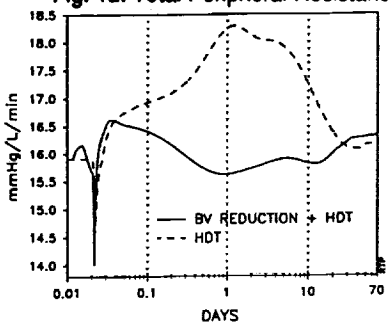


Fig. 13. Capillary Pressure

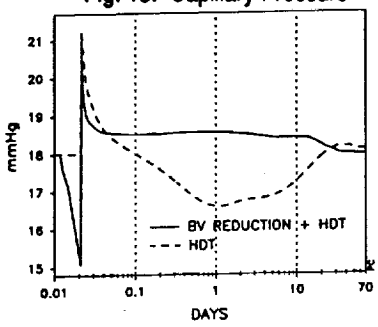


Fig. 14. Interstitial Fluid Pressure and Systemic Lymph Flow

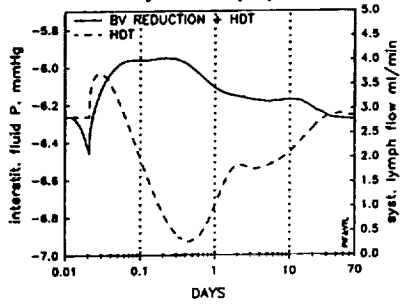


Fig. 15. Transcapillary Pressure and Flux

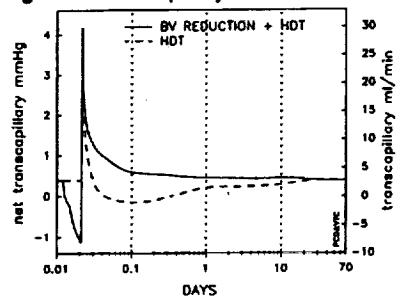
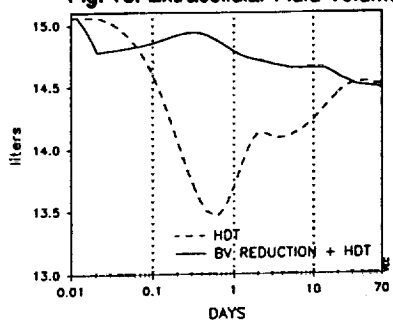


Fig. 16. Extracellular Fluid Volume



The results indicate how preadaptation of the circulation to a reduced blood volume appropriate for the weightless environment may be an effective countermeasure to much of the fluid losses observed in weightlessness. Simulation showed that pre-HDT reduction of the red cell mass prevents the hemoconcentration and increased blood viscosity that increases total peripheral resistance and shifts the balance of Starling forces toward net microcirculatory reabsorption. This prevents the large "undershoot" of extracellular fluid volume and the smaller "undershoot" of blood volume. However, the final equilibrium volumes are the same whether or not the circulation is preadapted. It therefore appears that the red cell mass drives the intervening "undershoot" of body fluid volumes but does not cause the resetting of the body fluid volumes at lower levels.

Experimental subjects will vary in their physiologic makeup and starting conditions, and consequently they will vary in their responses to fluid shifts. We do not yet have sufficient data to properly validate the entire time courses of the responses we have modeled, although the SLS-1 data do broadly suggest that there is an early drop in body fluid volumes with some later recovery that is also reflected by our Guyton model output. Our simulation began with subjects in a baseline supine position, rather than the upright ambulatory posture, and we did not model the effects of a prelaunch semisupine posture or the tendency of some astronauts to voluntarily dehydrate themselves before launch, as these vary greatly between individuals. Therefore the time course and absolute magnitudes of the changes in variables presented here should be regarded as qualitative rather than quantitative, pending further knowledge of physiologic responses to weightlessness that may be integrated into the model.

In conclusion, we used the modified Guyton model as an analytical tool to determine the primary determinants of the reduction of body fluid volumes in weightlessness. Results show that this process is initiated by a central volume shift that increases atrial volumes and pressures. The central volume expansion provokes a series of physiologic responses that cause a rapid return of central volumes and pressures to baseline through a reduction of the plasma volume. We conclude that the primary determinant or driver for an "undershoot" of body fluid volumes after the normalization of atrial volumes and pressures is the red cell mass.

REFERENCES

Charles JB, Bungo MW. Cardiovascular research in space: considerations for the design of the human research facility of the United States space station. Aviat. Space Environ. Med. 1986;57:1000-1005.

Epstein M, DeNunzio AG, Ramachandran M. Characterization of renal response to prolonged immersion in normal man. J. Appl. Physiol. 1980; 49:184-188.

Gaffney FA. Cardiovascular adaptation to 0-G: results from spacelab life sciences one (abstract) Aviat. Space Environ. Med. 1992;63:439.

Guyton AC, Coleman TG, Granger HJ. Circulation: overall regulation. Ann. Rev. Physiol. 1972; 34:13.

Kimzey SL. Hematology and immunology studies. In: Johnson RS, Dietlein LF (eds). Biomedical Results from Skylab. NASA SP-377, Sup. of Documents, Washington, D.C., 1977;249-282.

Kirsch KA, Röcker L, Gauer OH, Krause R. Venous pressure in man during weightlessness. Science 1984;225:218-219.

Lathers CM, Charles JB, Elton KF, Holt TA, Mukai C, Bennett BS, Bungo MW. Acute hemodynamic responses to weightlessness in humans. J. Clin. Pharmacol. 1989;29:615-627.

Leach CS. A review of the consequences of fluid and electrolyte shifts in weightlessness. Acta Astronaut. 1979;6:1123-1135.

Leach CS. Fluid control mechanisms in weightlessness. Aviat. Space Environ. Med. 1987;58:A74-79.

Leach CS, Alfrey C, Suki WN, Leonard JI, Rambaut PC. Fluid-electrolyte regulation during space flight. In: Nicogossian AE (ed). Spacelab Life Sciences-1 180 Day Preliminary Results. NASA Johnson Space Center, Houston, TX. 1992; pp 3.3.3-1 to 3.3.3-16.

Leach CS, Johnson PC. Influence of spaceflight on erythrokinetics in man. Science 1984; 225:216-218.

Leonard JI, Grounds DJ. Modification of the Long Term Circulatory Model for the Simulation of Bed Rest. NASA Contractor Report (NASA CR-160186), Washington, D.C., 1977.

Leonard JI, Rummel JA, Leach CS. Computer simulations of postural change, water immersion and bed rest: an integrated approach for understanding the spaceflight response. The Physiologist, 1979;22:S31-32.

Leonard JI, White RJ, Rummel JA. Math modelling as a complement to the scientific inquiry of physiological adaptation to space flight: fluid, endocrine and circulatory regulation. In: Hunt J. (ed). Proc. of 2nd Intl. Conf. on Space Physiology, Toulouse, France, 20-22 Nov. 1985, ESA publication no. SP-237, Paris, 1986;233-244.

Mukai CN, Lathers CM, Charles JB, Bennett BS, Igarashi M, Patel S. Acute hemodynamic responses to weightlessness during parabolic flight. J. Clin. Pharmacol. 1991;31:893-903.

Nicogossian AE. Biomedical challenges of spaceflight. In: Deltart RL (ed). Fundamentals of Aerospace Medicine. Lea & Febiger, Philadelphia, 1985;839-861.

Nicogossian AE, Parker JF Jr. Space Physiology and Medicine. NASA SP-447, Sup. of Documents, Washington D.C., 1982;186.

Nixon JV, Murray RG, Bryant C, Johnson RL Jr, Mitchell JH, Holland OB, Gomez-Sanchez C, Vergne-Marini P, Blomqvist CG. Early cardiovascular adaptation to simulated zero gravity. J. Appl. Physiol. 1979;46:541-548.

Simanonok KE. Effects of hypovolemia on the responses to water immersion in men. In review.

Simanonok KE, Bernauer EM. Blood volume reduction as a countermeasure to fluid shifts in water immersion. In press.

Simanonok KE, Srinivasan R, Charles JB. Computer simulation of preflight blood volume reduction as a countermeasure to fluid shifts in spaceflight. Proceedings of the Fifth Annual Space Operations, Applications, and Research Symposium (SOAR 91), Houston, Texas, July 9-11, 1992;605-608.

Simanonok KE, Srinivasan RS, Charles JB. Preadaptation of the circulation by removal of different blood volumes to counteract central fluid shifts. The Physiologist 1992;35:S111-S112.

Thornton WE, Moore TP, Pool SL. Fluid shifts in weightlessness. Aviat. Space Environ. Med. 1987;58:A86-90.

Thornton WE, Ord J. Physiological mass measurements in Skylab. In: Johnson RS, Dietlein LF (eds). Biomedical Results from Skylab. NASA SP-377, Sup. of Documents, Washington, D.C., 1977;175-182.

White RJ. A Long-term Model Of Circulation: Final Report. NASA Contractor Report (NASA CR-147674), Washington, D.C., 1974.